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Thesis :

Epidermophyton
interdigitale

by

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EPIDERMOPHYTON INTERDIGITALE

# INTRODUCTION

Were Epidermophyton interdigitale to appear in print for the edification of the general public, very few of the countless thousands afflicted with the commonly designated "Athlete's Foot" would recognize the disease under its biological name. The headlines threatening the dire consequences of the disease that have been found in most magazines during the last decade or longer have aroused the interest of many unsuspecting victims. Only very infrequently are the consequences as disastrous as they are pictured. Although none of the well-advertised medicaments or treatments have been proved successful, the infected persons have at least waked up to a realization that they are harboring an active fungus in their epidermis. Finding in most cases that the "sure-cures" promised in the advertisements do not clear up the condition, doctors or dermatologists have been consulted and have given more appropriate treatment.

History

1837 The earliest recorded mention that we have of a ringworm infection is that of Remah. He recognized the fungus hyphae in scutula of favus but did not realize that the fungus was the cause of the disease. For some time people could not agree whether the presence of the fungus was causal or resultant.

1845 Malnisten accepted the fungus as the causal organism and gave it the generic name of Trichophyton.

1860 Hebra recognized and named Hebra Eczema Marginatum although he associated it only with the groin. Kolobler, Peck, and Kaposa claimed the disease to be of mycotic origin.

1870 Tilbury Fox, an Englishman, associating the disease with improper functioning of the sweat glands, called it dysidrosis.

1884 Robinson, considering the disease an herpes of neurotic origin, called it pompholyx.

1890 Sabouraud established the plurality of ringworm fungus and began his very thorough investigations by careful clinical study and full notes, microscopical examination and culturing every case.

1892 Djelaleddin-Moukhtar saw the fungus of Hebra Eczema Marginatum in a foot and thought that the fungus had invaded the eczema.

1905 Castellani showed that "dhobie itch" contracted by

Americans in the Philippines was a variety of Trichophyton.

1907 Sabouraud isolated and described Epidermophyton inguinale.

1910 Sabouraud in "Les Teignes" brought together all previous work and research. This book is the foundation of all later work on ringworm.

1912 Jadassohn associated hand and foot lesions.

1916 Ormsby and Mitchell called the attention of American dermatologists to the prevalence and importance of the disease.

Sabouraud's contribution to the study is probably the most important so far. His early investigations were so careful and thorough that the publication of "Les Teignes" in 1910 gave a complete picture of ringworm as it was known and understood at that time. His "proof medium" was the most, if not the only, successful culture medium up to quite recent times. He was the first to use Epidermophyton as a generic name showing that it grows only in the horny layer of the epidermis attacking neither the hair nor the hair follicle.

Since 1916 the United States has become more fungus-conscious and particularly so since the World War. There are a number of dermatologists in this country who have done exhaustive research on one phase or another of the infection. While they have not all agreed in the conclusions drawn there is a much wider knowledge of the field and its possibilities.

There is as much disagreement on the method of infection and transmission as on any other point. The Canadians tend to the theory that it is not contagious, that it results from a condition of the epidermis, while the United States dermatologists advocate paper shoes, foot baths in gymnasiums, and other precautions against contagion.

## Geographical Distribution

Epidermophyton interdigitale is omnipresent throughout the world though the fungus may pass under different names in different sections. According to Fraser (1937), Kurotchkin thinks that Epidermophyton inguinale is most common in Europe while Reiss finds Trichophyton interdigitale the fungus most frequently involved in Shanghai foot infections.

The geographical distribution of the species is responsible for great variation in pathogenicity, for example, the fungus which develops a foot infection in the Pacific coast vicinity is less difficult to eradicate than the fungus infections prevalent in this part of the country. In hot countries such as Porto Rico the infection spreads from toes and hands all over the body. The disease is particularly prevalent in the tropics and warmer climates, there being little or no seasonal variation. Although the disease is widespread in western China where shoes are worn, among the collies who wear sandals or go barefoot the disease is practically non-existent. If the theory of the contagiousness of the infection is accepted--students coming to this country from China, India, and Japan where it is very common may have played a part in the spread of the fungus. An Edinburgh doctor (Percival, 1937) maintains that the hundreds of American students studying in that city do not transmit the infection, for the number of cases of the disease is not great. There are occasional outbreaks but they quickly subside; probably the cooler

climate inhibits the fungus.

It was the most common cause of skin diseases during the World War. A thorough study of the cases in a large number of Northern and Central European countries showed the greatest incidence then but there has been a gradual decrease since that time. It is much more prevalent in the southern part of our country, though the rest of the United States and Canada report many cases in summer and early fall. Eighty percent of the population of Texas is infected during the bathing season and a Houston doctor (Micheal, 1923) finds that it comprises from fifty percent to sixty percent of his practice. A Boston doctor (see Greenwood, 1922) claims it is four and one-half times as common in this part of the country as any other form of fungus foot infection.

Its greatest incidence is found in groups of young men, particularly those using common bathing facilities all or part of the time. In many colleges and universities there is anywhere from fifty percent to ninety percent of the student body infected, while as high if not a higher incidence is found among prisoners, soldiers, and sailors. The disease is very prevalent among the men and officers of the Royal Navy as well as our own. The United States sailors and marines who are greatly troubled with it in the tropics find that it disappears on their return to the States only to reappear when they return to the warmer countries.

## The Causitive Organism

The pathogen is a fungus which may cause different and distinct mycoses as it attaches itself to different parts of the body. Although this fungus has been cultured from other parts of the body it is generally found on the feet.

The classification from Dodge is as follows:

Group: Fungi Imperfecti

Family: Trichophytoneae

Genus: Epidermophyton Sabouraud

Species: Epidermophyton interdigitale

The Fungi Imperfecti is an heterogeneous group made up of fungi whose life cycles are incomplete and little known. The members of this group pass through an unlimited number of generations without any evidence of sexual reproduction, multiplying by conidia, oidia or chlamydospores. No sexual organs have been found to aid in placing the fungi in their correct groups. Those which resemble each other in appearance are placed together in one genus,. with the result that a genus may include widely separated fungi. When the complete life history is known a fungus is placed in the group in which it belongs.

The Trichophytoneae are parasitic almost exclusively on the horny layer or other keratinized structures of the skin. Dodge (1935) thinks that they are probably imperfect stages of Gymnoascaceae. The spore forms that are present include arthrospores, chlamydospores, closterospores, and aleurospores.

The spores are sessile or on short sterigmata borne on undifferentiated vegetative hyphae.

Sabouraud's classification of the members of this group is based on the relationship between parasite and host. Other classifications have been suggested using lesions, morphology, and media as bases. So far Sabouraud's classification has proved the most satisfactory and is the one most generally used. Confusion has resulted in many cases because certain striking characteristics have been used to classify the fungus rather than a consideration of the pathogen as a whole.

While the lesions may be formed on any portion of the horny layer each species generally confines itself to one keratinized structure; Epidermophyton interdigitale invades the sodden skin between the toes, Epidermophyton inguinale the inguinal fold, Trichophyton tonsurans the hair. The fungus produces only mild evanescent lesions, varying with the organism and its position in the epidermis.

Sabouraud was the first to use Epidermophyton as a generic name indicating that the fungus grows only on the horny layer, not invading the hair or the hair follicle. Closterospores are abundant, chlamydospores less conspicuous and aleurospores rarely found in this genus.

In this species there are several closely related fungi or identical fungi which have been given different names. The etiological study of the lesions has not been thorough enough

to clear up the confusion in the classification of this species. The following is a list of the different names of Epidermophyton interdigitale (Priestly) Mac Carthy:

1. Epidermophyton inguinale Sabouraud pro parte
2. Trichophyton interdigitale Priestly
3. Sabouraudites interdigitalis Ota and Langeron
4. Trichophyton gypseum var. 2 Ota
5. Trichophyton gypseum var. C. Hodges
6. Epidermophyton variable Karrenberg

Dodge puts the following here also:

7. Trichophyton interdigitale var. Kaufmann-Wolf Ota
8. Trichophyton granulosum Kamabayaski
9. Trichophyton gypseum var. 3 Ota
10. Epidermophyton inguinale Kurotchkin and Chen

The common names for Epidermophyton interdigitale vary with the part of the world in which it is found and the portion of the body which it infects. Every ship and station has its characteristic name for the disease. The term "ringworm" covers all superficial dermatomycoses. The lesions are approximately circular and grow with nearly equal rapidity in all directions, similarly to the fairy rings in mushrooms, so the ancient Greeks named the disease "herpes." The particular species in which we are interested was called by the Greeks "Herpes desquamans." The Romans, associating the disease with lice, called it "tinea." Our common name

"ringworm" is a combination of these two. "Tinea" is the medical term by which the infection is generally known.

In the tropics the disease appears under the name of "Mango toe," "Hong Kong toe," "Cantlie's foot tetter," or "Shanghai foot." The soldiers who returned from the Cuban invasion brought back "Cuban itch." The men who went to the Philippines at the time of the Spanish American War contracted "Dhobie," or "Washerman's itch." The name acquired during the World War was "toe itch." The disease has also been known as "toe rot," "golfer's foot," "fungus foot," or "toe scald," all terms more or less suggestive of the effects of the disease.

## Habitat Outside the Body

There are many theories concerning the habitat of Epidermophyton interdigitale, but there is little or no adequate scientific proof for its existence and growth outside the body. Authorities suggest different locations as ideal and all are agreed upon several conditions such as, moisture, warmth, and food supply if there is to be any growth. For mere existence in the spore form, these would not be necessary. The United States Public Health Service (1928) stressing the contagiousness of the disease lays the blame on bath mats, infected soap, and towels. The Public Health Engineering Section of the American Public Health Association (1930) claims that most, if not all, the fungus foot diseases are spread by infection from floors of dressing rooms, swimming pools, bath houses, gymnasiums and other places where people go barefoot. Under the lattice work of floors, on drain boards, in cracks, or wherever hair, slime, algal growth, and skin scales might be found in a moist and warm environment, would prove possible habitats for the fungus.

Growth outside the body has not been proved culturally in spite of many attempts that have been made. Bonar and Dryer (1932) made thirty to forty plants of scrapings from floor, hair, traps, etc., finding a great overgrowth of other organisms but no Epidermophyton interdigitale. Williams (1934) at Massachusetts Institute of Technology made fifteen hundred cultures from all the material or apparatus with which a

person using a gymnasium would come in contact. From these cultures he found only two colonies that might have been Epidermophyton interdigitale or inguinale though he could not be sure that they were either. There were numerous colonies of fungus growth which Williams suggests may be a pleomorphic form in which the fungus occurs outside the human host, changing to the customary form when it comes in contact with the human host. As there are comparatively few cases of "Athlete's Foot" at Massachusetts Institute of Technology, this might be considered a poor place for experimentation. Sharp and Taylor (1928) at the University of California found that carpets unused for many months yielded cultures.

Attempts have been made to grow the fungus on different substances with varying results. Bonar and Dryer (1932) experimented with growth on various woods, bricks, and blocks of cement. There was no appreciable growth on Douglas fir or pine in six months but weathered wood showed a slight growth, while boards, bricks, and cement blocks, well covered with an accumulation of slime, showed a very rapid development of the fungus. Sterilizing the algal growth or drying the culture for six months did not prevent growth. The colonies that showed no growth were recultured and found to be alive.

Epidermal cells continuously dislodged in the course of activities around gymnasiums are composed of a nitrogenous substance which makes an ideal food for the fungus. The fungus grows in and on strands of wool and silk, digesting them,

but it does not attack cotton or linen, apparently preferring animal to vegetable fabrics. Growth on leather and feathers, as well as silk and wool, is extensive, so it is possible that clothing may transmit the fungus, if it is transmittible.

## MORPHOLOGY

Dodge (1935) describes the species Epidermophyton interdigitale in culture as a whitish colony, becoming pale yellowish green but never pink or reddish. The growth of the colony is rapid, forming a pale buff boss with the rest white. On glucose media the reverse side of the colony varies from chestnut brown to black in the center with a yellowish margin. The fungus is inoculable into experimental animals.

The appearance of the surface of a colony depends on the spore forms produced, they in turn are dependent upon the age of the colony. Closterospores are the most typical organs of the group although their morphologic significance is not clear. When the complete life history is known they may be found homologous to some structure associated with sexual reproduction or they may be wholly asexual spores. The closterospore, borne on a septate, relatively coarse mycelium is a multinucleate structure, soon dividing into two, three, four or five cells each with the same number of nuclei. As the colony degenerates the closterospores are replaced by chlamydospores.

When the colony is composed primarily of chlamydospores it has a moist, glabrous, almost yeast-like appearance. Chlamydospores, a term used for different types of spores, are large, spherical and double contoured and carry the fungus over unfavorable conditions.

Aleurospores give the colony a powdery, chalky appearance. They are always uninucleate, the nucleus dividing two or three times before the daughter nuclei migrate into the germ tubes. The aleurospore is homologous in function to the conidium of Gymnoascaceae. Engrappes, aleurospores clustered like bunches of grapes, and fuseaux, large multicellular fusiform spores, are infrequently seen.

If the colony is composed of sterile mycelia it has a loose, cottony appearance. Spirals composed of delicate hyphae, either loosely or tightly coiled like the tendrils of a grape vine are occasionally seen.

Arthrospores are found both in lesions and in cultures. They are really undifferentiated hyphal cells which appear in rows when the environment is unfavorable. They have no morphologic significance as they are found in wholly unrelated groups.

There is a variation in the morphology of members of the same species. Spring (June, 1931) studied these variations in hanging drop cultures and considered them probably due to slight differences in humidity, oxygen supply and the size of the plant. Spring (July, 1931) also studied two strains of Epidermophyton interdigitale for heterothallism in an attempt to find an explanation for the variation in the same species. Single cells from aleurospores were inoculated on suitable media and the spores from these cultures were placed in a parallel position on a second

culture but no heterothallism could be positively distinguished.

It is very difficult to make positive generalizations concerning the morphology of this species. Different investigators and even the same investigator procure varying results under apparently identical conditions. Characteristics are not permanent, for practically all of them disappear in subcultures. A temperature change from twenty degrees centigrade to thirty-seven degrees centigrade produces decided color changes in the colony, but these color variations are not consistent.

Microscopic study is important when the identity of the fungus is in question but unfortunately the results of the microscopic examination do not always agree with the clinical and cultural pictures. Under such circumstances the dermatologist can only rely upon the indications which seem strongest. A study of the two hundred fifty-nine patients at the United States Veterans Hospital showed that all had clinical manifestations of "Athlete's Foot" but only a few were microscopically positive. Although stain may cause distortion of the material on the slide it is considered an aid to the diagnosis if there is any question of confusing the mycelia of the fungus with the so-called mosaic fungus. Ordinarily it is not necessary to use stain unless the slide is to be preserved.

The skin scale to be studied is treated with five

percent potassium hydroxide, then washed with water. It is then placed on the slide, the cover glass is pressed down, and the preparation heated slightly. If the scale is to be stained a drop of lacto-phenol cotton blue is placed with the scale on the slide. The epidermal cells stain light blue and the protoplasm of the fungus dark blue. The fungus should appear as a mass of anastomosing mycelial strands, more or less straight with rectangular segmentation. The strands are sometimes branching or they may be broken up into a chain of fragments. Even though the threads may be broken they always give the appearance of a chain. Although the fragments have been called spores they are generally acknowledged to be hyphae, the vegetative part of the fungus. Sexual reproduction must take place outside the human host, for the vegetative forms are the only ones found in the host. The vegetative mycelial forms found in human tissue are practically all alike, so recognition of species and genera lies in the manner of growth in vitro and in vivo, and in recognition of various spore forms.

There are three artifacts which simulate fungi: crystals, fat globules, and mosaic fungi. The crystals may be due to imperfections in the cover slips or they may be in the scales themselves caused by the kind of clearing agent used. The potassium hydroxide may form crystals which take the shape of the fungi in long anastomosing mycelial-

like growths. They have spore-like segments, as do the actual hyphae. They may be distinguished from the real fungus because (1) the threads lack uniformity; (2) there is no protoplasmic content in the cells; (3) there is an irregularity of outline not found in the actual mycelial threads. The crystals may be washed away and the true fungus remains.

When fat globules are acted upon by potassium hydroxide they are very like the so-called spore fragments and at times give the appearance of budding. They may be distinguished from the fungus cells by (1) extreme variability in size; (2) lack of regular septations such as the fungus has; (3) no cell content. Immersing the scales in ether before mounting in potassium hydroxide will break up the fat globules.

The third artifact and the most difficult to eliminate is the mosaic fungus. Ever since its discovery in 1888 by Ries it has been the subject of controversy, having been labelled in turn, a product of inflammatory tissue, keratohyaline, fat, free fatty acid, soap, degenerate fungus, and true normal fungus.

When a slide is treated with methyl salicylate and absolute alcohol the former brings out the actual fungus and the latter dissolves the mosaic. Xylene causes the mosaic to be clearly seen. The skin scales from fifty healthy persons showed this mosaic fungus formation which would indicate that it might be present in all skin scales

or in the slide preparations. If the mosaic was a degenerate fungus one would expect to find a form part way between the normal and the mosaic fungus. This intermediate stage has been carefully sought for on slides but has never been found. Other differences are marked; for example, the mosaic does not grow on culture mediums and lacto-phenol has no effect on fungus material while it causes the mosaic to disappear.

It is frequently difficult to get positive cultures of Epidermophyton interdigitale from parts of the body where its presence is suspected or even from material in which the fungus has been identified microscopically. It may be necessary to make one hundred plants before any appreciable growth of the desired fungus is found. The skin scales from vesicular areas provide better plants than those from squamous areas. The scales should not be taken from recently medicated portions of the feet as the drugs used may have an inhibiting influence on the growth of the fungus.

After the plant has been made there is frequently so great a contaminating growth of saprophytic molds and of pus organisms that the identification of the actual fungus is often impossible. Pathogens are downy white or faintly tinted while the saprophytes are deep green, brown, or black. The latter have a fuzzy appearance and they are more rapid growers. Drying for several days or soaking the skin scales in seventy percent alcohol will lessen this growth.

Until recent times Sabouraud's proof medium (one and one-half percent agar, one percent peptone, four percent dextrose, pH 5.6) was the medium generally used because it supported life longer and induced luxuriant growth. In fact, the growth on Sabouraud's proof medium is often too dense for easy identification of the fungus. Four percent maltose or four percent glucose may be substituted for the dextrose in the medium. During the War when it was difficult to procure the French sugars it was found that American pure dextrose served equally well. A medium with high ammonia concentration ends the growth of the culture at once because of the high pH. It is practically impossible to find a medium which will duplicate conditions as they are found in vivo.

Williams (1937) called attention to the fact that the materials in Sabouraud's proof medium are unlike the tissue on which the Epidermophyton interdigitale grows in the body. Williams uses a "W" medium (four percent peptone, one percent dextrose, one and one-half percent agar, pH 5. 6.) and finds that there is less pleomorphism on this than on Sabouraud's medium. Southworth (1937) has found a medium which produces a profuse growth of the fungus and varies much less than media containing peptone. It is composed of

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| Water | 1,100.0 c.c. |
| Dextrose | 40.0 gm. |
| Magnesium sulphate | 0.5 gm. |
| Potassium dihydrogen phosphate | 3.0 gm. |
| Dipotassium hydrogen phosphate | 0.5 gm. |
| Sodium chloride | 1.0 gm. |
| Agar | 15.0 gm. |

Urea 10.0 gm.

The pH is about 5.7.

Cultures of the same fungus vary greatly on different media. On maltose the growth is downy, slightly eccentric, and the color of an unripe lemon. It is composed of hood-like buttons surmounted by a tuft and divided by radiating furrows. On media containing sugar most cultures take a pleomorphic form (a return to the vegetative). This is a fluffy white overgrowth of hyphae which does not produce spores. It is necessary to use a medium without sugar (three percent peptone, one and one-half percent agar) to preserve a culture without this pleomorphic growth.

Slant tubes and Erlenmeyer flasks are used because Petri dishes do not give sufficient depth of the media. The plants are cut from dried skin scales and placed on the media. To lessen the growth of other organisms and molds the scales may be flamed and washed in alcohol before planting. Gentian violet (1:500,000) in the medium has the same result. Cultures are grown at room temperatures and when growth is well started transplantings are made to different media. For rapid development the fungus may be grown in a hanging drop preparation of glucose bouillon and mounted in glycerine.

The temperature which the fungus can withstand varies somewhat depending on the culture media used. Experiments were made by Bonar and Dreyer (1937) to study the

thermal death point of the fungi. Cultures were grown on agar slants until there was abundant sporulation, then some of the fungus material was shaken in a sterile tube containing one cubic centimeter of distilled water. This spore suspension was planted on culture media and heated to various temperatures for ten minutes, then cooled by immersing in ice water. The cultures were incubated at room temperatures for fourteen days. Growth was evident on all cultures heated up to fifty degrees centigrade. As the higher temperatures were tried, an increasing number of plants gave negative results. At seventy-five degrees all were negative. Epidermophyton interdigitale indicated greater resistance to heat than other closely related species. Mitchell (1922) maintains that the fungus is not destroyed by boiling in fifteen percent potassium hydroxide. These experiments give some indication of the effect that modern laundry methods might have on the fungus.

It is very difficult to get a positive culture from the blood of an infected person. Weidman and Spring (1928) report one thousand two hundred and sixty-nine blood cultures from more than seven hundred patients with only two positive results.

Pleomorphism is a gradual degeneration occurring in all dermatophytes and on all media to a greater or less extent. A colony develops normally from four to six weeks. When the colony has reached maximum growth white downy tufts,

known as pleomorphic growths, appear on the surface. Generally they appear first in the center and spread rapidly, covering the whole surface. The spores formed gradually decrease in number and are more simple in form. The first indication of degeneration comes when the spindles become less numerous and show less differentiation while the aleurospores and chlamydospores are more numerous. Finally these degenerate and the colony is composed of a downy mycelium of fine, vacuolated, sterile hyphae.

The pleomorphic mycelium is different from the normal mycelium, the hyphae are longer and finer and the mycelium is completely sterile. The protoplasm contains many more vacuoles and fat globules. If the normal culture is not completely degenerated elongated hyphae may produce small, little-differentiated, sessile, lateral spores. Occasionally chlamydospores are formed; otherwise there is no indication of spore formation. A pure pleomorphic culture has never been known to revert to the normal form.

A carbohydrate medium and a temperature from thirty degrees to thirty-seven degrees centigrade are most favorable to pleomorphic growth, while a nitrogen medium tends to prevent it. A pleomorphic culture may take any of three forms, any one reversible to either of the others: (1) a downy white culture, (2) a brownish glabrous culture or (3) a coarse shaggy culture.

Tate (1929) states that any of the pleomorphic forms

inoculated on animals develop as normal fungus growths. On recultivation from infected scales the fungus continues the pleomorphic growth from the interrupted stage.

No one has been able to show the cause of pleomorphism and authorities differ as to the procedure. Tate (1929) made an essential point of the fact that the same species always gives rise to the same pleomorphic forms. Emmons (1932) found two strikingly different pleomorphic forms derived from a single spore. There is such a decided difference between the normal and the pleomorphic forms that a fungus listed as a distinct species may be only a pleomorphic form of an already well-known species.

## Physiology

When food is plentiful the colony grows rapidly and no spores are formed, for the important function of the fungus is the development of mycelia. This activity goes on as long as the environment is favorable. As the food supply, pH, or moisture decreases spore formation begins. The pH range most favorable for growth is from five to six. The physiological features that make the skin ideal for the growth of the fungus are listed by Strickler (1931) as follows:

1. Storehouse for large amount of dextrose,

2. Fairly constant ratio between the dextrose content of the skin and of the blood,

3. Presence of diastatic and glycolytic enzymes,

4. Existence of lactic acid, an important product of carbohydrate metabolism, normally present in the skin,

5. Presence of dextrose which increases formation of lactic acid,

6. An increased amount of sugar in sweat which makes a more favorable environment.

Sweat, the carrier of this rich food, can come in intimate contact with the epidermal cells or any intercellular substance that may be present for there are no limiting walls to the sweat duct. The sweat glands themselves, although they are more active, show no pathologic changes. An increased production of sweat is generally associated with the increased activity of the fungus or with the spread of the disease. As clinical improvement is shown, the sweat secretion becomes more normal for the sweat is no longer needed

to remove the toxic and metabolic products of the fungus.

The organism requires complex organic nitrogen compounds in order to live; these are found in sweat and in epidermal cells but not in cellulose. The fungus survives and probably thrives on silk, wool, leather and feathers, provided there is enough moisture present.

The action of the fungus is threefold: (1) it eliminates a keratolytic ferment resulting in a corrosive action on the epidermis; (2) it causes growth resulting in an irritant action; (3) it has a toxic influence.

Goddard, (1934) in his studies of the metabolism of the fungus, found that hexose, glucose, pentose, arabinose, fructose, mannose, and disaccharide maltose were assimilated producing a slight increase in weight. Lactose and sucrose were assimilated in very small amounts or not at all. In every case the pH was increased independently of the sugars present. Glucose decreased the rate of protein hydrolysis but did not decrease the formation of ammonia from amino acids. The result was a higher pH. Casein and peptone support growth and are hydrolyzed to polypeptides, amino acids, and ammonia. In peptone or sugar-free culture there is a gradual disappearance of protein nitrogen and the appearance of peptide nitrogen during the first three weeks of culture growth. At the end of thirty days the protein nitrogen is gone, the peptide nitrogen decreased, and the ammonia nitrogen greatly increased as shown by a rise in pH. During the last period there is a

great increase in size of the colony. On glucose-peptone medium the action is more rapid. At the end of twenty-one days the growth reaches its maximum weight and there are many spores formed. After three days the spores germinate. The growth of the fungus cannot continue because of the accumulation of waste products or because the available food supply in the medium is consumed. During the period of rapid growth twice as much glucose is consumed as the increase in the weight of the fungus shows. The amino acid nitrogen concentration depends on the rate of the peptone and peptide breakdown to free amino acids and the rate of assimilation and respiration of these acids by the fungus.

Williams and Southworth (1937) have studied the effect of salts on different pathogenic fungi and have found that sodium acetate and sodium sulphate inhibit the growth of the fungus, while sodium chloride has very little effect upon it. Phosphates incorporated in the medium increase the development of spores and lactates have the same effect on the development of mycelia, according to experiments by Weidman and Spring. (1928)

## Type of Person Involved

Epidermophyton interdigitale seems to show little selective preference for any one group or class of people outside those previously mentioned as sailors, soldiers, prisoners, and habitués of gymnasiums, though there are some types of employment in which one finds a pronounced tendency toward the infection. Cleanliness does not seem to be an absolutely necessary precaution, for the disease is rarer among the poorer people who bathe less frequently and live under less ideal conditions than the well-to-do. One reason for the latter class having greater known incidence may be that a rich person having time and money would be more apt to consult a doctor for a disease that was causing only slight discomfort or inconvenience, while a poorer person, although having the use of free clinics, would not trouble himself about such a minor inconvenience. If all cases were reported there might easily be as many among the poorer classes but that would not make cleanliness an essential factor.

The reason that so much of it is associated with gymnasiums and swimming pools may be that men and women who use them would in many cases be subject to physical examinations, at which time the disease would be recognized. As they go into the pools with bare feet the presence of the disease would be called to public attention if it is at all conspicuous.

There seems to be little tendency for people of any one

race to be more susceptible than those of another. The incidence among negroes is about the same as among white people, and, although it is very prevalent in India and some parts of China, the living conditions as well as the climate would tend toward widespread infection.

Some doctors warn against familial infection but the majority feel that the disease is acquired not through contagion but rather because of lack of resistance in the skin. If it is transmitted from person to person an inanimate intermediary is necessary. As there have been cultures of Epidermophyton interdigitale made from scales of apparently normal healthy skin, it would seem possible that the fungus is always on hand waiting for some opportunity to enter a breach in the epidermis.

In Williams' (1936) summary of the 2,400 cases of dermatophytosis at the Boston City Hospital since 1926 he classifies the occupations of the infected patients. Although in no cases were there enough in any one occupation from which to draw any sweeping conclusions, the results are interesting. Those with high incidence of involvement of the feet are laborer (70), clerk (25), chauffeur (16), salesman (16), custodian (15), shoeworker (14), carpenter (12). The people listed above all came from the city and the incidence among country dwellers might be quite different, though the people who work on the land would be more nearly like the laborers who have the highest incidence.

It is interesting to note that chauffeurs are included in this list for I have noticed that after driving several hundred miles my sister findsthat her right foot, which is almost continually on the accelerator, has a particularly active case of "Athlete's Foot."

The great majority of the people who are infected with ringworm are between the ages of sixteen and sixty. The Epidermophyton infection is very rarely found in children, though there are other kinds of ringworm quite prevalent in childhood. The greatest incidence is probably among people in their twenties and thirties. Old people, being much less active, would be unlikely to have the disease.

According to most statistics the foot infections are much more common in men than in women due to a number of different factors. Women's footwear is lighter, more aerated, more frequently changed, and offers less opportunity for the accumulation of perspiration. These conditions overbalance the fact that women's shoes are much snugger on the feet. Women take better care of their bodies and in general their work is less strenuous. The greater incidence of involvement of hands among women may be a question of allergy. Some of the infections may be primary but in most cases they are probably secondary. The primary infection may pass unnoticed and the hands would be the most likely place in women for a secondary infection.

There are, as with other diseases, ringworm carriers but

as the contagiousness of the disease is in doubt one questions their importance.

## The Infection

The actual method of infection is not known although several conditions necessary for its continuance are recognized. A number of different mold-like fungi live on the skin normally, leading a saprophytic existence until some trauma or local injury to the skin gives them opportunity for entrance.

The infection, in order to develop, must have a sufficient number of viable pathogens and the skin must have a lack of sufficient immunity. To continue growth the infection requires moisture, more or less darkness, a reduced oxygen supply, a warm temperature, and food. The fourth interdigital space offers a very acceptable location and the macerated skin, practically always found there, a continuous food supply. The nail of the fifth toe is a constant irritant on the skin in the interspace. The sweat secreted here is more concentrated and provides the necessary hydrogen concentration. Weidman (1927) was unsuccessful in his search for a specialized sebaceous gland that might account for the sensitiveness here.

The shoes, interfering with the normal desquamating process, keep the skin moist and soft, especially between the toes. We are more careless about our shoes than about any other part of our clothing, wearing the same shoes for months without disinfection or internal cleansing.

Orthopedic foot disorders in many cases occur with ringworm infection, the most frequent one being flatfoot. In

flatfoot there is a relaxation and depression of the bony structures in the foot, causing an unnatural pressure on the muscles, tendons, nerves, blood and lymphatic systems, thereby decreasing the circulation. The result of these changes is a lowered skin resistance and an increased chance that it will become infected with the fungus more easily. Lieberthal and Lieberthal (1934) studied fifteen cases of ringworm associated with flatfoot. Ten of the cases had advanced vesiculopustular lesions on the soles and in the intertriginous spaces resistant to all treatment and five of the cases were moderately serious responding only slowly to treatment. All fifteen cases were treated for flatfoot and when that was corrected they all responded to treatment for the ringworm infection. In three patients the infection disappeared.

Dysidrosis is in many instances associated with the infection whether in the position of cause or effect is not known. Wearing shoes that are too short or in any way place the foot in an abnormal position gives rise to mild discomfort in which an increased amount of sweating is marked.

As the ringworm infection grows in the epidermal layers inflammation is not marked unless there are other types of infection or an invasion of the dermal layer. The fungi are of a hardy stock, growing in varieties of room temperature though they prefer warmth. They can easily pass into a saprophytic form and become pathogenic when the environment is favorable.

The vesicular and squamous types are found primarily in

the upper two-thirds of the stratum granulosum always among the partly or completely cornified cells parallel to the surface. Mycelia have been found as deep as the tenth epidermal layer. The fungus never penetrates the cells but forms an intricate network about them. The infection spreads to the other interspaces and occasionally to the sole or dorsal surface of the foot, or the nails may become infected. Infection in any part of the body can in most cases be traced back to a former, apparently cured, or to a latent case in the interdigital position.

As the disease spreads to different parts of the foot it takes on diverse forms. These vary from an acute discharging sore to the very slight and often unrecognizable infection in the epidermis. The latter is much the most common and in its least serious stage is hardly more than a superficial peeling of the skin between the toes or about the nail. Different dermatologists classify the varying forms in somewhat similar ways.

1. Macerated, desquamous, squamous, exfoliative or chronic. In its lighter forms there is little more than the peeling of the skin in the interdigital spaces. As it becomes more active the skin in the fissures becomes dark grayish red. In the interspaces are found large macerated skin scales. The horny layer separates and it is easily pulled off. Vesicles, if present, are formed in the subcorneal layer and similar lesions in the stratum malpighii. There may be some

surrounding inflammation, but very seldom. This form is confined to the interdigital spaces.

2. Vesicular type is composed of small blisters with a clear syrupy discharge. There is never any pus formation except from a secondary infection such as staphylococcus or streptococcus. According to Sabouraud (1911) the "essential lesion....a vesicle, may be solitary or multiple, grouped or widely disseminated. The vesicle, deeply seated, only slightly elevated, has the appearance of a sago grain embedded in the epidermis." These vesicles have walls made up of the surrounding epidermal cells and a roof of stratum corneum alone, or, in addition, several layers of stratum granulosum. Surrounding these cells are many polymorphonuclear leucocytes. The syrupy liquid found in the vesicles is made up of fibrin, fragments of epithelial cells, and polymorphonuclear leucocytes. The cells of the true skin discharge a substance made up of polymorphonuclear leucocytes and lymphocytes, found mostly in the papillary and the subpapillary layers directly beneath the vesicles. The nearby blood vessels are normal. These vesicles are found anywhere in the vicinity of the toes and in acute cases they may spread anywhere on the foot. As the vesicles dry the top cracks and peels off leaving an area of pinkish new skin with a margin of loosened scales. New vesicles form near the old ones, leaving a rounded gradually increasing area of new skin as they, in turn, dry.

3. Eczematous type is red and oozing, formed when the

vesicles or pustules break before they dry. This form has more inflammation, is characterized by intense itching, and may extend beyond the interdigital position.

4. Hyperkeratotic form appears on the plantar surface and may or may not be associated with vesicles. There is a noticeable thickening of the horny layer which may crack and peel off.

5. Lichenoid form, rarely seen, is caused by continued scratching of an area which is infected.

There is in all the types skin cracking and fissure formation; generally vesicles are present although they may be deeply embedded in the epidermis. Itching and burning are associated with most forms and pain with the more acute. The greatest difference between the squamous and vesicular types is in the degree of intensity.

## RESULTS

In the human body there is a greater degree of cutaneous allergy than is generally recognized. As ringworm is one of the commoner infections the understanding of its allergic reactions is important. There are instances when this allergic reaction can be traced back to the poison released by Epidermophyton interdigitale and instances when the source is uncertain. It is possible that the so called secondary lesion may have the same infector as the primary lesion.

The essential feature of the allergy is the altered sensitivity which permits a minute amount of fungus or even a toxin to produce a conspicuous lesion. These allergic manifestations may be caused by the fungus in several ways: (1) by fragments of fungus elements from within; (2) fungus elements from without acting as antigens; (3) toxins formed by the fungus; or (4) a combination of any two or all three of these. In (1) and (3) the fungus fragments and toxins are transported to various parts of the body by the blood stream. The secondary infection may be general or localized, either near to or far from the original infection. The only explanation for the localization of the secondary infection is some skin injury at that particular point. Scratching or contact with infected clothing may aid in making the hand the frequent seat of the secondary infection or in making the hands the means of transmission by (2).

When these fragments of fungus elements or their toxins

come in contact with the living skin they initiate a hypersensitivity with its widespread allergic reactions. A person may be sensitive to organisms and their toxins from his own body and not sensitive to those produced in vitro. The longer the infection has been present in the horny layer, the greater the hypersensitivity produced when the organism reaches the dermis. The deep as well as superficial infections produce the same degree of sensitivity. As these organisms or toxins circulate they come in contact with immune bodies which deaden them. To reach the epidermis at the site where the secondary infection is to be located they must pass through hypersensitized skin, which destroys most of them. For this reason the fungus element is rarely found in a secondary infection.

The secondary reactions are referred to as "ids": epidermophytids, trichophytids or dermaphytids. They are actually a sterile manifestation in the sensitized skin of the presence of a fungus elsewhere in the body. The epidermophytids may appear as eczema, urticaria, asthma, or hay fever. Scrapings from epidermophytids give negative microscopical results though very occasionally a fungus of great virulence can pass through all barriers and give rise to epidermophytosis in the secondary infection. Williams (See Traub and Tolmach, 1933) reports that in the very early stages of a typical transient lichenoid epidermophytid and in a vesicular epidermophytid fungus

elements have been found.

There are several characteristics of an epidermophytid which will aid in diagnosis.

(1) It does not increase in size as a primary lesion does.

(2) It, with a very few exceptions, does not contain fungus elements demonstrable microscopically or culturally. If one does reach the point of secondary infection it is generally killed by allergic skin.

(3) It has a preference for follicular skin.

(4) It must be associated with a primary lesion, generally found between the toes. If there is no primary lesion in evidence there may be a history of an organism there.

(5) It requires the presence of a caustive agent in the primary lesion. This organism should be proved pathogenic culturally or microscopically or both.

(6) It should give a positive trichophytin reaction, showing that the disease is not local.

(7) It should make its appearance at least several months later than the primary lesion. It may even be several years later, depending upon the site and the host.

(8) It should be sterile.

Williams (1937) considers allergy "an honest attempt of body cells to produce protective bodies which has failed because of their inability to respond with an efficient

weapon." He continues discussing the contraction of the disease, "our chance . . . depends upon the ratio of allergy plus dosage to that of tissue immunity plus acquired immunity." The allergic antibody, instead of becoming an immune antibody, has developed into a substance harmful to the tissues. A knowledge of the relationship between allergy and immunization is important as an aid in understanding skin infections.

Skin eruptions may be due to pathogenic fungi or to an allergic reaction. It is never safe to apply any treatment until the identity of the cause is determined, as the treatments for the two differ fundamentally. The use of an active fungicide such as would be applied to a fungus infection only aggravates the area of allergic reaction or may set up a generalized allergic reaction. "Ids" must be treated with as little irritation as possible, it is better to leave doubtful lesions untreated. The complete eradication of primary infection generally clears up the secondary infection spontaneously.

Skin which has been sensitized by fungus infection will be much more sensitive to other substances such as dyes, metals, fabrics, soaps, and chemicals. This fact plays an important part in compensation. Trichophytin allergy belongs to a large and universally important group of allergies of great practical importance in infections diseases.

Allergy is generally assumed to be specific, not toward one species, but toward a whole group.

There seems to be little or no immunity conferred by an attack of ringworm infection. The latent stage that the disease may go through probably has nothing to do with immunity but is the result of external conditions such as lack of food or moisture. In considering the relation between allergy and immunity Williams (1937) states that there are certain cells in the body strong and healthy enough to develop immune bodies for their protection; whereas other cells less well endowed develop allergic antibodies. Vaugha (1936) carries it farther, maintaining that the protective bodies are the same for allergy as for immunity; the latter act with maximum efficiency while the former act abnormally. Certainly the cells in the epidermal layer would be less strong and healthy and as a consequence unable to produce the immune bodies.

Attempts have been made to desensitize the skin and build up an immunity with gradually increasing doses of trichophytin. This treatment has been used only in very severe or obstinate cases. The results are quite uncertain as some patients have shown improvement, others have been worse, and still others unaffected by the treatment.

It is only infrequently that the fungus exerts an influence strong enough to be actually disabling. Probably

only a small fraction of one percent of the number of persons infected is sufficiently incapacitated to be unable to work. The itching and burning sensations may be decidedly uncomfortable; only infrequently is the pain severe enough to hinder walking. The very occasional acute case may mean disability for varying lengths of time, anywhere from a few days to a year.

The more serious occupational effects result from secondary infections which may be caused by the entrance of other pathogens through the lesions made by the ringworm infection or may be of allergic origin. Scratching may transfer the infection directly to other parts of the body or allergy resulting from the infection may render the skin more sensitive to chemicals. Wise and Wolf (1936) feel that foot lesions are too frequently associated with lesions found on other parts of the body. Nevertheless a good dermatologist in diagnosing skin eruptions on the hands examines first the interdigital spaces of the feet.

The disease is important industrially from the point of view of compensation. The laws regarding compensation for occupational injuries vary in different countries and in different states. England and Germany have no laws regarding such benefits. In this country no compensation is allowed for the initial primary infection unless it can be proved to result from some contact in the industrial plant concerned. The chronic recurring infection which is aggravated by heat

and moisture, a condition common to everyone and to all industries, is not subject to compensation. When an industrial dermatitis is responsible for the spread of the chronic ringworm infection or when the ringworm infection is made more acute by the presence of an occupational skin condition, compensation may be claimed. If a mycotic infection immediately follows an industrial dermatitis it is compensatory as it is held a sequel arising from the worker's employment.

If the employer wishes to safeguard himself it is quite important that his employees be given a thorough examination before they are hired for any work that might result in skin diseases. There are such a great number of cases of latent or chronic infection, which if they are not recognized before hiring, may be claimed to have originated as a result of the occupation.

## Treatment

In spite of the widespread incidence of "Athlete's Foot" its activities are in many instances at subclinical level or can be kept there. The suggested treatments are many and varied; from kerosene and chiropractic for the affected parts to tonics and high vitamin content diet for the general condition. Some of these treatments are beneficial, some are injurious and the rest, when they do not hinder natural improvement, are more or less harmless. Many of the well-advertised medicaments have been shown to have absolutely no inhibiting effect on the growth of the fungus on culture media. Some dermatologists advocate electro-magnetic rays of different kinds, others claim they do more harm than good. So that any treatment that may be suggested is more or less in the line of an experiment, it may be successful or it may not be.

Most dermatologists are agreed that it is a disease almost impossible to eradicate completely with a certainty of its non-return. There are treatments so irritating to the skin of a particular patient that the result is much more incapacitating than the disease itself. Self-treatment may add other diseases or lower the resistance of the skin to such an extent that the skin will not be able to carry out its protective function. Reaction to different medicaments varies to so great an extent with each patient that treatment must be individualized.

Remedies to be of value must be such that they can

penetrate the superficial strata of rete and they must be strong enough to destroy both mycelia and spores. A medicament which is effective in vitro may have no effect on the fungus in vivo. There are several reasons for this difference between test tube and clinical results:

1. The physical difficulty of delivering enough of any given drug to the site of infection.

2. The tendency of the drug to combine more readily with epidermal structures than with the organisms present.

3. The possibility of some type of tissue reaction induced by application of the drug.

4. The tolerance of the individual toward any one particular drug.

5. The inactivation of the drug by the solvent.

Laboratory tests can be valued only as suggestions. Occasionally some drug will have a clinical success not shown in vitro because of some type of tissue reaction induced by the drug.

There are two fundamentals of treatment: First, the elimination of factors favoring growth, such as moisture, accumulation of macerated skin, constant irritation caused by shoes or socks; and second, the avoidance in the application of medicaments of too active a drug on infected areas or of any drug on allergic areas. It is much safer to start with a very weak solution and if the skin shows no ill effects increase the concentration. The treatment to be used depends upon the form or stage of the disease at the time of application. If the infection is chronic or mild more active treatment can be

used than would be advisable if the disease were in the vesicular or eczematous form. If improvement stops, another medicament may be tried as the flora becomes temporarily immune to a drug. Long continued treatment, if it is not too severe, gradually sterilizes the skin.

Whitefield (1911) became accidentally infected on the arm. At first he tried an extremely strenuous treatment, scrubbing the infected area until it bled and then painting it with tincture of iodine. The next day it was painted with pure carbolic acid and after three weeks the scab fell off and the ringworm infection commenced to grow again. Whitefield then rubbed in an ointment of benzoic and salicylic acids in a soft paraffin and cocoanut oil base. The infection disappeared after the third day of this treatment. These are the chemicals used in the well-known Whitefield's ointment.

Whitefield's ointment is used as frequently and probably as successfully as any other one medicament in this country, but this cannot be used by all patients for it is irritating to some skins. It is a treatment for the disease in its less active stage. There are other similar ointments and salves that are advocated by various dermatologists. Some doctors alternate different treatments; strong tar ointment and chrysarobin are used alternately with Whitefield's for the chronic cases with macerations and fissures. Buchbinder (1934,2) finds that cresophan used two or three times a day for fifteen minutes usually clears the most obstinate cases. Wet compresses

or antiseptic soaks followed by ointments are good. Stronger lotions and powders can be used for chronic cases.

For lesions in the more active stage less stimulating treatments are required. Potassium permanganate and silver nitrate used on the vesicular form tend to convert this exudative condition into the squamous stage. Weak aluminum or lead subacetate solutions cause the rapid drying of vesicles, while silver nitrate and half-strength tincture of iodine, are successful for scattered vesicles. This vesicular type is apt to be overtreated with salicylic acid and ointments which contain salicylic acid. Bland ointments can be used on keratolytic types and pumice stone or sandpaper on calloused types.

The general formula for treatment is as follows: (1) Removal of epithelial debris and corneal layer, as well as tops of vesicles and pustules; (2) destruction of fungus by certain drugs depending upon the form of the disease; (3) alteration of cellular activity by electro-magnetic rays; (4) prophylaxis, the continued use of ointments or drugs after apparent cure.

Sargent (1937) reports the following treatment for a one hundred percent outbreak of "Athlete's Foot" aboard a United States navy ship. The treatment was given daily for one month, then three times a week for two weeks, and finally twice a week for six weeks. Each man was given ointment. He then took off his shoes and socks, turning the socks inside out. While the patient rubbed his feet, especially between the toes,

with the ointment two corpsmen put formalin in the shoes and two others put castnac powder on the foot part of the socks. Deek's, Whitefield's, phenylmercuric nitrate, and salicylic acid and sulphur were the ointments used.

As preventative measures rubber mats replaced wooden gratings and a ten percent solution of sodium thiosulphate was placed in galvanized iron foot tubs in front of all showers. All socks, underwear and towels were boiled in the laundry. The men were not allowed to walk in their bare feet and had to wear white cotton socks. Eighty percent of the men were cured at the end of the three month period. Incidentally soft corns were cured by the treatment.

In an Albany Junior High School (Gould, 1931) in the fall of 1928 it was found that hundreds of the students had "Athlete's Foot." Ninety-seven percent of those infected had the mild desquamating type, the remaining three percent had the vesicular and eczematous kind. The latter group was forbidden to use the swimming pools and the gymnasiums. Swabbing with iodine and mercurochrome-220 soluble did not check the condition. The next year fifty percent of the pupils were excluded from the gymnasium because of their foot infections. In November, foot baths containing ten to fifteen percent sodium thiosulphate were installed and four weeks later the infection disappeared. The foot bath reaches all parts while swabbing does not. A twenty percent powder of sodium thio-

sulphate and boric acid was tried with success on feet, shoes, and socks.

In choosing a medicament Weider (1934) considers the following factors;

(1) Is it as effective in vivo as in vitro?

(2) Does the patient have tolerance for that particular drug?

(3) Is the drug inactivated by other chemicals in the preparation?

(4) Can it penetrate the infected areas?

(5) Is it specific for the species of fungus present?

(6) Is the drug toxic for the species of fungus present?

(7) Does the drug tend to decrease moisture and maceration?

(8) Will its use produce other, possible more harmful, skin diseases?

Ointments are generally used for the infection when it is in the chronic or mild stage.

1. Whitefield's

| | |
|---|---|
| Benzoic acid | 5 parts |
| Salicylic acid | 3 parts |
| Soft paraffin | 8 parts |
| Cocoanut oil | 30 parts |

The salicylic acid in the ointment acts as a keratolytic, removing the horny layers of the epidermis before the fungus has opportunity to penetrate the next layer. It is used when all signs of acuteness are gone. Strong tar ointments may be alternated with Whitefield's for the chronic stage with macerations and fissures. There are certain skins that are intolerant to this preparation so the initial application

should be made with that in mind. The ointment may be diluted with vaseline, increasing the strength as no irritation results. Precipitated or colloidal sulphur, essential oils, or thymol may improve its usefulness but should be added cautiously as irritation may result. Whitefield's ointment causes the skin to thicken and scale giving a corrugated appearance.

2. Swartz's ointment

| | |
|---|---|
| Salicylic acid | 2. grams |
| Mercurochrome | 68. grams |
| Hydrous wool fat | 16. grams |
| Petrolatum | 16. grams |

This is a modification of Whitefield's ointment which gave very good results, in cases followed by Dodge (1935) personally.

3. Chrysarobin

| | |
|---|---|
| Chrysarobin | 20 parts |
| Sulphuric ether | 100 parts |
| Acetone | 100 parts |

This ointment is used extensively in England and France, occasionally in this country. The fact that it stains is a disadvantage.

4. Mycozol, a Parke Davis preparation, is most successful after scales have been removed.

5. Hydrophen ointment (orthophenylphenolmercuric nitrate made with aquaphor base) is very highly spoken of by Rein and Rosemblum (1937). They made comparative tests of hydrophen and Whitefield's on one hundred prisoners and forty-five private patients with more satisfactory results for hydrophen. It was preferred because it was cleaner to use, similar to

vanishing cream, more antipruritic, and gave better results, decreasing sweating and maceration.

6. Phenylmercuric nitrate was used by Levine (1933) in ointment form on one hundred and ten patients with tinea of the feet and all were cured. Twenty-one of these patients had secondary infections of the hands which healed promptly. Seven of the patients were sensitive to phenylmercuric nitrate.

7. Pine and tar ointment (six percent crude tar and three to five percent pine tar) is mildly stimulating.

8. Ammoniated mercury ointment (five percent) is of value in acute cases if placed in and around the toes after drying.

| | |
|---|---|
| Ammoniated mercury | 10 parts |
| Wool fat | 5 parts |
| Yellow wax | 5 parts |
| White petrolatum q.s. ad | 100 parts |

9. Strickler's formula:

| | |
|---|---|
| Iodine crystals | 1.3 grams |
| Potassium iodide | 1.9 grams |
| Salicylic acid | 1.9 grams |
| Boric Acid | 3.8 grams |
| Alcohol (fifty percent) to make | 59.1 c.c. |

This formula is effective at times but generally disappointing in view of its fungicidal value in vitro.

10. Schamberg, Brown and Harkins (1931) after experiments with the constituents in vitro suggest the following ointment;

| | |
|---|---|
| Oil of cloves | 0.06c.c. |
| Oil of cinnamon | 0.06c.c. |
| Iodine | 0.03 grams |
| White petrolatum q. s. | 33. c.c. |
| Zinc oxide may be added if desired | |

Lotions are frequently made up with the same essential ingredients but their liquid form makes them more usable under

certain conditions. They are used in subacute and acute cases.

1. Potassium permanganate in varying dilutions. This is very often used in the more acute cases as it hastens the drying of the vesicles.

2. Abracide skin lotion 1:100

3. Four percent salicylic acid and eight percent resorcinol in alcohol solution.

4. Two percent acetic acid.

5. Burow's solution (alum and lead acetate)

6. Pine oil compounds; alpha-terpineol, white pine oil, and very pale yellow pine oil.

Dyes have in many cases been found effective.

1. Wright's stain (methylene blue and methyl alcohol, weak protein coagulants) probably kills the fungi by fixation and staining the cells. It will not penetrate the deeper layers of tissue but is painless and soothing.

2. Fuller (1937) finds the following formula effective.

| | |
|---|---|
| Methylene blue | 50 grams |
| Glacial acetic acid | 125 grams |
| Ethyl alcohol, (ninety-five percent) | 2375 c.c. |

3. Crystol resorcin crystal violet hydrochloride is a new dye which has been found very successful in vitro.

4. Two percent gentian violet.

Dusting powders are of value in preventing moisture and to some extent as fungicides.

1. Castnac powder (Sargent 1937)

Liquor cresolis comp. 1.5

| | |
|---|---|
| Sulphur sublimed | 5.0 |
| Menthol | .5 |
| Camphor | .5 |
| Salicylic acid | 1. |
| Talcum q.s. ad. | 100. |

2. Two percent cresophan in boric acid aids in preventing reinfection.
3. One percent salicylic and benzoic acids, five percent boric acid in talc.
4. Four percent salicylic acid and eight percent resorcinol in talc.
5. Mycozol dusting powder.
6. One to two percent salicylic acid in talcum powder.
7. Fuller (1937) gives three formulas for powders that may be used interchangeably.

| | |
|---|---|
| a) Boric acid, in fine powder | 10 parts |
| Sodium thiosulphate, in fine powder | 10 parts |
| Talc or starch, in fine powder | 80 parts |
| b) Boric acid, in fine powder | 17 parts |
| Zinc stearate, in fine powder | 17 parts |
| Sodium borate, in fine powder | 33 parts |
| Talc, in fine powder | 33 parts |
| c) Salicylic acid, in fine powder | 30 parts |
| Boric acid, in fine powder | 100 parts |
| Talc, in fine powder | 870 parts |

For foot baths there are a number of preparations, some found successful under certain conditions, others not. It is important to use in these foot baths a fungicidal agent which will be effective for some time.

1. Ten to fifteen percent sodium thiosulphate; this solution is probably more frequently used than any other

although it is ineffective after forty-eight hours.

2. One percent sodium hypochlorite in a solution of chlorinated soda will destroy the fungus in five minutes in vitro. The solution deteriorates very readily and must be renewed daily.
3. Chlorox in one to five thousand dilution.
4. Two percent solution of liquor cresolis compound.
5. Cresophan in one to one thousand dilution.

Iodine was used very extensively and is still used by many dermatologists. It is of value only in so far as it penetrates the tissues on which the fungus is grown. Its parasiticidal effect on the fungus in vitro is stronger than that of any fungicide used. Iodine is used in a three percent tincture and also in compound solution. Wise (See Traub and Tolmach, 1932) claims five cents worth of iodine does more good than five dollars worth of anything else.

Castellani's (1928) basic fuchsin paint is used very effectively in warmer climates for resistant acute cases. It is prepared as follows:

To 10 c.c. of a saturated alcoholic solution of basic fuchsin is added 100 c.c. of five percent aqueous carbolic acid solution. This mixture is filtered and 1 gram of boric acid is added. After standing two hours 10 grams of resorcinol are added. The solution is then allowed to stand another two hours before adding 5 c.c. acetone.

It is applied daily or oftener with a cotton wad.

Formalin has germicidal properties second only to those of bichlorate of mercury. It is a powerful coagulant of cell proteins, producing a leathery condition on the skin. The cells are destroyed without the formation of pus. The application is irritating to the skin, producing a moderate gnawing and smarting pain in the lesion. Formaldehyde is very frequently used as a disinfectant for shoes. Care should be taken that it does not produce a formalin dermatitis.

The widely advertised Absorbine Jr. has no effect on the fungus in vitro during a thirty minute period. Ordinary soap has no value but germicidal soap may have.

Trichophytin, a fungus antigen, is similar to the tuberculin used in the tuberculosis of the skin. That trichophytin is not a specific and that its actual value is questionable are admitted by practically all dermatologists. Its attempted uses are threefold; first, as a test to show the presence of the fungus infection; second, as a medicament for its therapeutic value; and third, as a medicament for its prophylactic value.

Trichophytin is prepared without heat or chemical treatment because heat and chemicals denature the antigen to such an extent that the response of the antibodies of the host is changed. Mass cultures of the fungus are washed and ground in the special type of ball mill which breaks the fungus into fragments. This emulsion is filtered through a special ultrafilter and the filtrate is used for testing as well as therapeutically and prophylactically.

This antigen preparation does not show the presence of the fungus unless the infection is deep seated but it does, in most instances, reveal the presence of allergy toward fungus products. The reaction to the trichophytin may be positive for an epidermomycosis apparently cured if the allergy remains. When the process is superficial the toxicity of the fungus is low and if toxins are not absorbed by the system or if organisms do not produce immune bodies allergy will be absent and the test negative.

Tolmach and Traub (1933) examined thirty-eight patients with clinical diagnosis of epidermophytosis of the feet or hands or both. Twenty-three of them showed a positive trichophytin test. Seven patients had fungi in the lesions on the feet and vesicular or squamous lesions of the hands diagnosed as epidermophytids. From all seven one would expect a positive trichophytin reaction but in each case the response was negative. Williams and Carpenter (1932) found five cases out of seventy in which the test was negative but fungus had been recovered. These can be accepted as actual cases of fungus infection, with every indication of the presence of allergic reaction, giving the negative test.

There are several possible reasons for a negative trichophytin test when the fungus is actually present; (1) number of pathogens may be small, (2) pathogens may have been destroyed by inflammation, (3) fungus may have low viability or poor development, (4) pathogens may be in a state of anergy,

and (5) toxins may not have been absorbed by system.

If the trichophytin extract is contaminated with bacteria a false positive test may result. There is no relation between the severity of the infection and the response to the test. A patient may give continued negative reactions in different sites but a positive reaction if an original site is retested.

If the trichophytin test is specific then negative results might indicate that the hand lesions are eczematous or of ectogenous origin and the foot lesions would have no association with them. If the trichophytin test is not specific then there is no sure means of distinguishing eczema, dysidrosis, and epidermophytids.

There are still some dermatologists who advocate the use of trichophytin as a vaccine but they are very few in number. Novak (1925) gives injections of trichophytin and trichon* in addition to the usual treatment for very severe cases. It is generally conceded that the use of the extract either therapeutically or prophylactically is more injurious than beneficial. There may be isolated cases in which the skin may be desensitized by its use but the usual result is to increase the allergic reaction rather than decrease it. The use of trichophytin extract has given generalized manifestations of an allergic nature which take the form of urticaria, hay fever, asthma, or an aggravation of existing epidermophytids.

Trichophytin may be an aid in the identification of

* An autolyzed preparation of the trichophyton

epidermophytids but it can hardly be called infallible. A positive test when the presence of secondary infections are suspected is of value as a check but a negative test does not prove that the lesions are not associated epidermophytids.

Roentgen rays or X-rays are beneficial in the following ways: (1) they make the action of the drug more rapid when used with it; (2) they promote the absorption of the infiltrate; (3) they inhibit dysidrosis; (4) they stimulate the skin but do not kill fungus; and (5) they modify the skin so that it is less favorable to fungus growth. The ray treatment has its limitations and dangers: (1) too much radiation may cause damage to the skin; (2) there is no definite fungicidal value; (3) it tends to develop dermatophytids. The ultraviolet rays have a desquamating effect and a definite fungicidal value, similar to exposure to the sun.

These electro-magnetic rays are strongly advocated by some dermatologists. In the Philippines they have been proved effective but are too expensive for general use. In this country they are used in conjunction with other medicaments and aid in shortening the course of the disease.

More dermatologists are coming to believe that the first and most important treatment is proper foot hygiene. Moisture should not be allowed to accumulate in the interdigital spaces. The spaces should be carefully dried after bathing and dusting powder should be applied. Careless wiping fails to remove offending organisms. Loose skin should not be

allowed to collect. Proper well-fitted shoes, with no area that gives irritation, are important. The socks should be light weight and frequently changed. A dusting powder should be shaken into socks and shoes. Sandals or some type of open-work slipper should be worn whenever possible. Any foot disorders such as flat-foot should be corrected.

## PREVENTION

For the prevention of the initial fungus infection there is no hard and fast rule that can be followed with a certainty of success. Cleanliness alone will not cure but it does aid in preventing common infection. Soap has no destructive action on the fungus but it lowers the surface tension of the water and facilitates the complete wetting of all particles. The feet should not be exposed when there is chance for infection. The use of foot baths may act as a preventative measure, their prophylactic value rests on the chance that the organisms picked up by bare feet on the floors will be killed in the sterilizing solution. The solution of sodium thiosulphate most extensively used has been shown to have value in vitro but not in vivo. Fuller (1937) suggests replacing the sodium thiosulphate with a two percent solution of liquor cresolis hypochlorite. The necessity for keeping the interspaces in the feet dry and for removing all macerated skin from that position can hardly be overemphasized. If there is any possibility that the fungus may be present in the skin without giving the characteristic reactions it is important to remove at least two of the circumstances that aid its propagation. Certain dusting powders which tend to decrease the amount of sweating may be used prophylactically as well as therapeutically.

As the fungus finds certain fabrics, particularly silk and wool, suitable environment it is advisable not to use

the clothing of an infected person. Shoes which are worn continuously and may come in direct contact with an infection are considered by some doctors reservoirs for the fungus. To keep the feet dryer and overcome hyperhidrosis it is advisable to wear shoes with tops perforated by many holes. The fungus does not grow on rubber, so rubber bath shoes avoid the possibility of infection. W. R. Redden of the American Red Cross says: "Probably if we all wore thin stockings and sandals the problem would be solved."

It is generally assumed that locker rooms, showers, public swimming pools and gymnasiums aid in spreading the disease but Rein and Rosenblum (1937) find a higher incidence among prisoners who enjoy none of these luxuries than among habitués of gymnasiums and swimming pools.

Recurrence of "Athlete's Foot" or any similar fungus foot infection after apparent cure may be due to (1) renewed activity of an organism dormant in the epidermal layers or to (2) reinfection from external sources.

Sulzberger (see Jamieson and McCrea, 1937) claims that it has been conclusively shown that people who have this infection carry it on their feet throughout their lives. Mycelia have been found in the deeper layers of the epidermis some distance from the original lesion. Clinical cure is frequent under proper treatment but traces of the fungus can always be found in the horny layer.

Jamieson and McCrea (1932) examined one hundred cases

that had been pronounced clinically cured. The result of the microscopical examination showed sixty-seven percent of these positive although not all of the sixty-seven percent were culturally positive. The fungus spores may lie dormant for months, even years, and break into renewed activity as soon as the environment is favorable for their propagation. After one serious attack of the infection the precautionary measures that are taken are so through that there are comparatively few cases of reinfection severe enough to come under a doctor's care. Most of the cases are slight enough to receive self-medication by methods already learned.

There is always the possibility of reinfection from floors, swimming pools, showers and gymnasium equipment. Flushing the floors does not destroy the fungus growth that may be there, on the contrary it may aid in its propagation. To control the fungus growth on floors it is necessary to scrub and disinfect them.

Shoes as a source of reinfection have been carefully studied by Jamieson and McCrea (1937). There would be slight chance of contracting the disease from new shoes that might have been tried on at some previous time by an infected person. A person with an active case of ringworm would hardly be trying on shoes and a person with a latent case would have too brief a contact with the shoes to deposit any fungi, especially with stockings between. The shoes of fifty-two infected persons were examined and in only sixteen

cases were fungi found. The rapid growth of contaminating material may have prevented the identification of the fungus in some cases.

Bedroom slippers coming in direct contact with the feet would seem a much more probable source of reinfection. The slippers are made of material which may provide food for the fungus and the spores may be caught and held in the fabric. Swartz (see Jamieson and McCrea, 1937) was unable to identify any fungi in material scraped from the inside of the slippers.

If there is any possibility of shoes acting as a reservoir for the fungus, fumigation with formaldehyde is the best method of control. A teaspoonful in a castor cup placed in the shoe will be absorbed by the leather. It is better to place the shoe and its contents in a tightly covered shoe box for overnight. A wad of cotton saturated with formaldehyde and placed in the shoe has the same effect. Even though the shoes may not harbor any fungi this measure may be of value for when the shoes are worn the gradually released formaldehyde has a fungicidal effect on the lesions of the feet. Formaldehyde should be used cautiously at first as some skins are intolerant toward it.

Although most dermatologists are agreed that reinfection from without is possible they think that reactivation of latent spores is more probable. To control this it is only necessary to keep the fungus in a dormant state by

removing its requirements for growth and multiplication. Thin stockings or socks, changed frequently; correction for any foot disorders; careful drying, especially between the toes; all these are good prophylactic measures to follow. Occasional application of a medicament which has already been proved well tolerated by the skin is of value.

## Associated Diseases

There are several other Epidermophyton fungi that might easily be confused with interdigitale without microscopical and cultural study. None of them is as common or as resistant to cure as Epidermophyton interdigitale. Epidermophyton niveum has been found in the interdigital spaces and on the soles of the feet in a case of pseudodysidrosis. Epidermophyton gypseum was isolated from lesions on palms of the hands and soles of the feet. Both cases were chronic and resisted all treatment. Epidermophyton floccosum is interesting historically as the cause of Hebra Eczema Marginatum. This disease is confined chiefly to the inguinocrual fold and is most active in young unmarried males. Tinea barbae and tinea capitis are closely associated fungus forms which attack various parts of the body.

The dry, patchy squamous form may be confused with psoriasis or with the second and third stages of syphilis. The psoriasis is characterized by flat, superficial yellow pustules which dry to form brownish intraepidermal scabs. Syphilis is in the skin rather than the epidermis; there is no vesicle formation and no noticeable itching. Dermatitis venenata and eczema are found on the dorsal part of the hands, feet and fingers. Associated with both of these diseases we find inflammation and a serous exudation. Dysidrosis or pompholyx is characterized by burning sensations rather than itching. Impetigo, generally located on the face, is caused

by streptococci and contaminating staphylococci.

There have been a number of erysipelas eruptions reported in the literature recently. This disease is different from the real erysipelas because the attacks are shorter, prostration is less severe, and the sharp margin of the true erysip elas is lacking. Traub and Tolmach (1937) treated a patient who complained of an eruption of the lower part of the leg. A slight amount of scaling and fissure formation was found in the interdigital spaces. Skin scales from the interspaces were microscopically and culturally positive for Epidermophyton interdigitale. The blood culture was negative as were the tests for streptococci, staphylococci, and oidiomycin. The patient was treated with a fungus vaccine of Epidermophyton interdigitale and the eruptions on the leg disappeared. There are other epidermophytids occasionally seen, scarlatiniform exanthems and enanthems, erythrodermas, erythema, migrating phlebitis, urticaria, elephantiasic trichophytid, and lymphedema. Many of these will spontaneously disappear when the feet are treated for ringworm infection.

Chemical irritants may be confused with this fungus infection. Vesicular eruptions which had been treated for dermatophytosis of feet were found to be due to the dye in the socks or the chemicals used for tanning the leather. One or two cases have been reported as caused by shoe polish. These eruptions assume a vesiculo-bulbous appearance and affect the instep; the interdigital spaces are never the initial seat of

infection. The results of skin tests and the absence of fungi in the lesions should indicate the nature of the irritant. Chemical irritants more frequently involve the hands than the feet because the hands come in contact with a greater variety of chemicals. The allergic result of a fungus foot infection makes a person much more susceptible to the chemical irritant.

## Conclusions

In spite of all the work that has been done on Epidermophyton interdigitale there are many points on which dermatologists are not agreed. Various classifications have been proposed based on the relation between host and parasite, on morphological characteristics, and on the nature of the lesions.

The fungus may infect all of mankind; no race or color is exempt although there is a variation in the form that the infection takes in different parts of the world. Every climate has its "Athlete's Foot,"; throughout the year in hot countries, and with seasonal variation in cooler zones. Any or all classes of people may be involved, men more than women, and people in their twenties and thirties more than the young or the old. Any occupation or pursuit of pleasure which involves increased temperature and moisture in the pedal extremities is a factor to be considered, for the fungus can generally be found in moist, warm, dark, macerated parts of the body.

That the fungus is viable for short or long periods of time has been proved. What host alternates with the human host, what changes, if any, the fungus goes through outside the human body is unknown. It has been cultured from many animal substances but not in great quantities. On different culture media it takes a variety of pleomorphic forms, very different from the normal form. Outside the human host it may appear in unrecognizable pleomorphic forms.

The infection develops gradually and is, in most cases, unrecognized until a sudden flare-up makes one conscious of its presence. The actual method of infection is in doubt; some feel that direct contact with an infected person or his clothing is a certain way of contracting the disease. Yet there are surprisingly few cases of familial infection, but numerous instances of wholesale infection in high schools, colleges, gymnasiums, and prisons and on training ships. It would seem that in addition to a source of infection a certain skin condition was necessary. In instances of epidemic infection the occupation or relaxation offers opportunity for an unusual amount of exercise.

The fungus is found almost exclusively on the feet, particularly in the interdigital spaces, although it has been identified in other parts of the body. It takes on varying forms with the changes in season, occupation, environment, and foot care. Probably over ninety percent of the infections are in the macerated form. A larger percent might be found if all cases were reported. At times of undue activity or in the warm weather the chronic form may develop into the vesicular, subsiding again to chronic as conditions change.

The fungus has a toxic and an irritant action on the human epidermis which results in itching and burning sensations and occasionally pain. It may sometimes be painful enough to be disabling but its more serious effect comes

from secondary infections. It sensitizes the skin and makes it much more susceptible to other pathogens and to chemical irritants. The allergy which almost invariably accompanies a fungus foot infection may have results far more widespread than we now realize. Unfortunately the presence of the fungus develops no immunity in the human host and the fungus becomes active whenever conditions are favorable.

To make a comparatively sure diagnosis the fungus should be examined culturally and microscopically as well as identified clinically as there are other dermatoses which simulate the Epidermophyton infection. It may be difficult to find the fungus for microscopical investigation as it is not present in all the lesions. In studying the fungus under the microscope there are artifacts to be separated from the real fungus. It is even more difficult to grow a positive culture for the medium is so quickly covered with contaminating growth that the identification of the fungus is almost impossible. On most media the fungus takes on pleomorphic forms very unlike the normal growth.

The number of different treatments suggested is almost as large as the number of persons infected. Every doctor and dermatologist has his own pet theories as to the most effective way to treat the infection. As individuals differ so must treatments differ; a medication valuable in clearing the infection for one person may not be tolerated by the skin of another person. Whitefield's ointment and its modifications seem to be the most popular in this country for

chronic or mild cases. While potassium permanganate is most frequently used as a soak for vesicular forms. The X-ray and ultra-violet ray are of rather doubtful value, aiding the skin to control the fungus rather than affecting the fungus directly. Trichophytin is of little value except as an indication of the presence of epidermophytids, and that is not always certain.

Body hygiene is thought by the majority of doctors as the most important factor to be considered prophylactically and therapeutically. While clothing and other articles of wearing apparel may easily harbor the fungus, how important they are in the spread of the infection is a question. Once infected, always subject to reinfection, in spite of claimed clinical cures, is the belief of most dermatologists.

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